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(54) MEDICINAL PREPARATION

(57)Abstract:

PURPOSE: To obtain the subject preparation excellent in stability, capable of avoiding the hard dissolution of a medicine lowering its solubility in a neutral region, improving its absorbability in digestive tracts, and useful for controlling the release of the medicine, by covering a medicine agent comprising the specific medicine and an organic acid with a coating film comprising a polymeric compound.

CONSTITUTION: This preparation is obtained by covering (A) a medicinal agent obtained by granulating (i) a medicine lowering its water solubility in a neutral region together with (ii) an organic acid with (B) a coating film comprising a water-insoluble polymeric compound. The components (i) and (ii) are granulated in the presence of a bulkhead so as not to contact with each other, and the granule is formed in a structure wherein the components are arranged in the order of the components (i)-(ii)-(B) from the center of the preparation to the outside. The component (i) is preferably either of a thiourea derivative of formula I [R1,R2 are lower alkyl, group of formula II (R3 is H, lower alkyl; X, Y are 0-2); A is-CH:CH-, -CH=N-; 1 is 1, 2; m is 0-2; n is 1-51, noscapine, quinine, and cimetidine; the component (ii) is preferably either of citric acid, etc.



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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application]This invention relates to the medicinal preparation which can control discharge of a drug in order to acquire the continuous effect of a drug. It is concerned with pH and share stress in an alimentary canal, discharge of a fixed drug [be / nothing] can do the drug with which water solubility falls in a neutral region, and an absorptivity falls in detail at the time of internal use for this reason, and it is related with the medicinal preparation which was excellent in improvement in the stability for aiming at effective use of a drug, and a discharge rate further.

[0002]

[Description of the Prior Art]When it is the drug that water solubility falls in a neutral region, as a method of securing the solubility, the technique in which a solid solution is made to form is known. There is an example which blends a drug into a high molecular compound and is used as the sustained release drug as an amorphous state as a means to gradual-release-ize a drug using this method. However, it was difficult for the solid dispersing element for the solubility of the high molecular compound which constitutes it to rule over, or for the solubility by the side of acidity to be too high under the influence of gastric acid, or to secure stability.

[0003]As a method of gradual-release-izing, the salts which have a drug and a buffer action in the coat of insoluble in water nature polymers are blended, The method of using and gradual-release-izing that the solubility of a drug falls according to the increase in an organic acid content is known by blending organic acid with diclofenac sodium as the discharging control pharmaceutical preparation which is not influenced by pH by making pH in a coat regularity, and same art. however, such art -- any -- although -- it is the method of reducing solubility to a constant level, and is the method of raising the solubility of the drug that solubility falls in a neutral region, and the gradual-release-ized pharmaceutical preparation is not known.

[0004]Therefore, the purpose of this invention is to provide the medicinal preparation which can guarantee the bioavailability which was excellent in stability, could avoid refractory-ization in the neutral region of the drugs by which solubility falls in a neutral region, raised the absorptivity within an alimentary canal, and was excellent.

[0005]

[Means for Solving the Problem]This invention persons found out the following this inventions wholeheartedly as a result of research.

[0006](1) Medicinal preparation covering drugs produced in a neutral region by coming a drug with which water solubility falls with organic acid with a coat which consists of a high molecular compound of insoluble in water nature formed by spray coating etc.

[0007](2) Medicinal preparation given in the above (1) providing and coming a septum so that said drug and said organic acid may not contact mutually.

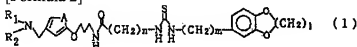
[0008](3) Medicinal preparation the above (1), wherein an internal structure of said medicinal preparation has the structure formed from the central part in order of a coat which consists of a high

molecular compound of organic acid-drug-insoluble in water nature towards the outside thru/or given in (2).

[0009](4) Medicinal preparation the above (1) in which said drug is at least one of a thiourea derivative expressed with a following general formula (1), noscapine, quinine, and the cimetidine thru/or given in (3).

[0010]

[Formula 2]



[0011]. [whether a low-grade alkyl group is shown, respectively by R_1 in [type and R_2 being the same or different, and] Or R_1 and R_2 become together and the basis which has $-(CH_2)_X-CHR_3-(CH_2)_Y-$ (R_3 in a formula shows hydrogen or a low-grade alkyl group, and X and Y show the integer of 0 **** 2) is shown, A shows $-CH=CH-$ or $-CH=N-$, l is 1 or 2, m shows 0 **** 2 integer, and n shows the integer of 1 **** 5.].

[0012](5) Medicinal preparation the above (1) which said organic acid becomes from at least one of citrate, succinic acid, tartaric acid, and the malic acid thru/or given in (4).

[0013](6) Medicinal preparation the above (1) whose ratio of said organic acid is 50 or more weight sections to said drug 100 weight section thru/or given in (5).

[0014](7) Medicinal preparation the above (1) whose coats which consist of a high molecular compound of said insoluble in water nature are an ethyl acrylate methacrylate [methyl] copolymer emulsion and/or ethyl cellulose thru/or given in (6).

[0015]Main gestalten of medicinal preparation of this invention are the medicinal preparation which separated by drug with which water solubility falls in a neutral region, and a microscopic septum, corned with organic acid, and covered this with a coat which consists of a high molecular compound of insoluble in water nature. this this invention -- gradual-release-izing of a drug of many for which gradual-release-izing was difficult until now, or control of discharge of a drug is attained.

[0016]In medicinal preparation of this invention, although organic acid helps the dissolution of a drug, with a basic drug which reacts to organic acid and is disassembled by one side, a septum contributes to reservation of stability in a state of preservation.

[0017]By what a relation of a coat which consists of organic acid, a drug, and a high molecular compound considers as structure which serves as a coat which consists of an organic acid-drug-high molecular compound toward the outside from the central part in medicinal preparation of this invention. Dissolved organic acid can dissolve a drug efficiently, a coat which consists of high molecular compounds can be made to pass and emit, and futility of organic acid is lost. Organic acid which a part dissolved as it is a reverse structure will not pass along a drug layer, but will be emitted, and does not contribute to the dissolution of a drug.

[0018]In medicinal preparation of this invention, although it is also possible to make this organic acid into an acid salt, since a lot of salts are needed as compared with organic acid, it becomes large-sized manufacturing medicine, in order to acquire sufficient solubility of a drug, and administration becomes difficult, usefulness of organic acid is more expensive.

[0019]By making it structure mentioned above, a drug unstable to organic acid can also carry out [****]-izing of the medicinal preparation of this invention so that a drug may moreover be used effectively easily.

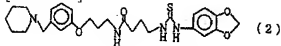
[0020]It is not a thing limited in any way as a drug mainly used for medicinal preparation of this invention, and a drug with which water solubility falls in a neutral region is mentioned. Basic drugs still more specifically expressed with a general formula (1), such as a thiourea derivative, noscapine, quinine, and cimetidine, are mentioned.

[0021]A thiourea derivative used by this invention mentioned above is crystalline powder which has an

antibacterial action and an antiulcer action to HEKORIBAKUTA pylori, and, generally is poorly soluble in a neutral region. TRM-115 expressed with the following general formula (2) as a classic example of this thiourea derivative, for example is mentioned.

[0022]

[Formula 3]



[0023]As organic acid used for this invention, if nonpoisonous to a living body, it will be good, for example, succinic acid, tartaric acid, citrate, malic acid, etc. will be raised. Loadings of organic acid should have only the quantity in which a drug is dissolved in a polymers coat, and, generally 50 or more weight sections of organic acid should just be in a drug to 100 weight sections.

[0024]As a high molecular compound of insoluble in water nature used as a coat used for this invention, an ethyl acrylate methacrylate [methyl] copolymer emulsion (marketing name: -- OIORAGITONE30D.) Rehm Pharma, ethyl cellulose, polyvinyl acetate, polyvinyl chloride, Although an aminoalkylmethacrylatecopolymer etc. are dissolved with a high pH solution (pH 6.5 or more), insoluble hydroxypropylmethylcellulose acetate succinate, methacrylic acid, a methyl acrylate copolymer, etc. are raised to water.

[0025]Within the limits of a limit defined by person skilled in the art, quantity (only coat) of a high molecular compound of insoluble in water nature can be fluctuated. Specifically, it is 1 to 30 % of the weight more preferably one to 50% of the weight to a granulation thing.

[0026]In medicinal preparation of this invention, although not limited at all as a microscopic septum between a drug and organic acid, powder coating, coating of a membrane formation nature substance, etc. are mentioned, for example.

[0027]As an ingredient which can be used for powder coating, what is necessary is just an excipient generally used for drugs, and milk sugar, starch, white soft sugar, grape sugar, mannitol, xylitol, sorbitol, crystalline cellulose, talc, etc. are mentioned.

[0028]The membrane formation nature substance should just be avirulence for a living body, for example, hydroxypropylcellulose, hydroxypropylmethylcellulose, methyl cellulose, a polyvinyl pyrrolidone, etc. are mentioned.

[0029]Otherwise in a coating agent as a septum mentioned above, acetylation monoglyceride, such as a plasticizer, Diethyl phthalate, a triacetin, triethyl citrate, acetyl triethyl citrate, tributyl citrate, propylene glycol, tributyrin, a polyethylene glycol, dibutyl sebacate, castor oil, etc. may be added. Talc, titanium oxide, etc. may be added as an antibonding agent.

[0030]Pharmaceutical preparation of immediate releasability [medicinal preparation / of this invention] (whether a soluble film is used for a coat of this medicinal preparation.) Gradual release speed is also controllable by mixing arbitrarily pharmaceutical preparation which covers a gradual release coat thinly or does not cover a coat (as a capsule etc. which filled a granule and this granule in a capsule) to such an extent that a releasing speed is not influenced.

[0031]Medicinal preparation of this invention is mainly used as an orally administered drug.

[0032]When considering it as pharmaceutical preparation generally used widely, such as a capsule for taking orally to Homo sapiens, and granulation, as a concrete dosage form of medicinal preparation of this invention, it is considered as spherical particles 500-2000 micrometers in diameter, and a method of filling up one capsule with hundreds of particles, and prescribing them for the patient, etc. are mentioned. It can be considered as a forcible administration agent for animals as a pill about 10 mm in diameter, or can use as drugs for fish as a sphere 10 cm in diameter.

[0033]A process of medicinal preparation of this invention is not limited in any way, and all of a mixing method of a drug, a formation method of a septum, a coating method of a coat, etc. can be performed in accordance with a publicly known conventional method.

[0034]Powder coating of an organic acid layer, a barrier layer, and the drug layer is carried out in layers,

carrying out the spray of the joint liquid to a spherical nuclear material as a concrete example, and a method of finally coating a polymers coat of insoluble in water nature is mentioned.

[0035]

[Example] Hereafter, an example is shown and this invention is explained still in detail.

[0036] (Example 1) Hydroxypropylcellulose was melted in dehydrated ethanol and 5% (w/w) of joint liquid-1 was obtained. Powder coating of the pin mill grinding thing of tartaric acid was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of joint liquid-1 to crystalline cellulose (grain) (cell FIACP305: Asahi Chemical Industry).

[0037] Powder coating of the milk sugar was carried out after desiccation, using CF GURANYU letter similarly as a septum. Powder coating of the powder which mixed TRM-115 and milk sugar by 1:1 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-1 containing OIDORAGITTO NE30D was coated with the fluid bed (STREA-1: Powrex) after desiccation, and the pharmaceutical preparation shown below was obtained.

[0038]- Joint liquid-1 hydroxypropylcellulose Five Part dehydrated ethanol 95 Part [0039]- Coating fluid-1 OIDORAGITTO NE30D 100 Part talc 30 Part purified water 170 Part [0040]- Formula core cell FIACP305 Ten 1st layer of part tartaric acid 20 Part joint liquid-1 7.2 copies of 2nd layer (septum) Milk sugar 60 Part joint liquid-1 26.4-copy TRM[3rd layer]-115 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-1 50 Part mean particle diameter 1000 - 1680 mum [0041] (Comparative example 1) The pharmaceutical preparation shown in the following prepared by the same technique as Example 1 was obtained except using milk sugar instead of tartaric acid.

[0042]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 1) of part

Milk sugar 30 Part joint liquid-1 33.6 copies of 2nd layer (the 3rd layer in Example 1)

TRM-115 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-1 50 Part mean particle diameter 1000 - 1680 mum [0043] (Example 2) Powder coating of the pin mill grinding thing of tartaric acid was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of the joint liquid-1 prepared in Example 1 to crystalline cellulose (grain) (cell FIACP305: Asahi Chemical Industry). Powder coating of the milk sugar was carried out after desiccation, using CF GURANYU letter similarly as a septum.

[0044] Powder coating of the powder which mixed TRM-115 and milk sugar by 1:1 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-2 containing ethyl cellulose 10NF was coated with the fluid bed (STREA-1: Powrex) after desiccation, and the pharmaceutical preparation shown below was obtained.

[0045]- Coating fluid-2 ethyl-cellulose 10NF 5 Part talc Four Part triethyl citrate Three Part ethanol 88 Part [0046]- Formula core cell FIACP305 Ten 1st layer of part tartaric acid 20 Part joint liquid-1 7.2 copies of 2nd layer (septum)

Milk sugar 60 Part joint liquid-1 26.4-copy TRM[3rd layer]-115 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-2 100 Part mean particle diameter 1000 - 1680 mum [0047] (Comparative example 2) The pharmaceutical preparation shown in the following prepared by the same technique as Example 2 was obtained except using milk sugar instead of tartaric acid.

[0048]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 2) of part

Milk sugar 30 Part joint liquid-1 33.6 copies of 2nd layer (the 3rd layer in Example 2)

TRM-115 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-2 100-copy mean particle diameter 1000 - 1680 mum [0049] (Example 3) Powder coating of the pin mill grinding thing of tartaric acid was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of the joint liquid-1 prepared in Example 1 to Nonpareil 103 (Freund Industrial). Powder coating of the milk sugar was carried out after desiccation, using CF GURANYU letter similarly as a septum.

[0050] Powder coating of the powder which mixed milk sugar with quinine by 1:2 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-1 prepared in Example 1 was coated with the fluid bed (STREA-1: Powrex) after desiccation, and the pharmaceutical

preparation shown below was obtained.

[0051]- Formula core Nonpareil 103 30 1st layer of part tartaric acid 60 Part joint liquid-1 21 The 2nd layer (septum) of part

Milk sugar 180 Part joint liquid-1 75 3rd layer of part quinine Ten Part milk sugar 20 Part joint liquid-1 15 Part coat coating fluid-1 270 Part mean particle diameter 1000 - 1680 mum [0052](Comparative example 3) The pharmaceutical preparation shown in the following prepared by the same technique as Example 3 was obtained except using milk sugar instead of tartaric acid.

[0053]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 3) of part

Milk sugar 30 Part joint liquid-1 33.6 copies of 2nd layer (the 3rd layer in Example 3)

Quinine 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-1 100 Part mean particle diameter 1000 - 1680 mum [0054](Example 4) Powder coating of the pin mill grinding thing of citrate was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of the joint liquid-1 prepared in Example 1 to crystalline cellulose (grain) (cell FIACP305: Asahi Chemical Industry). Powder coating of the milk sugar was carried out after desiccation, using CF GURANYU letter similarly as a septum.

[0055] Powder coating of the powder which mixed nescapine and milk sugar by 1:1 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-1 prepared in Example 1 was coated with the fluid bed (STREA-1: Powrex) after desiccation, and the pharmaceutical preparation shown below was obtained.

[0056]- Formula core cell FIACP305 Ten 1st layer of part citrate 40 Part joint liquid-1 14 The 2nd layer (septum) of part

Milk sugar 60 Part joint liquid-1 The 26.4-copy 3rd layer nescapine Five Part milk sugar Five Part joint liquid-1 7.5-copy coat coating fluid-1 28 Part mean particle diameter 1000 - 1680 mum [0057]

(Comparative example 4) The pharmaceutical preparation shown in the following prepared by the same technique as Example 4 was obtained except using milk sugar instead of citrate.

[0058]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 4) of part

Milk sugar 100 Part joint liquid-1 40.4 copies of 2nd layer (the 3rd layer in Example 4)

Nescapine Five Part milk sugar Five Part joint liquid-1 7.5-copy coat coating fluid-1 28 Part mean particle diameter 1000 - 1680 mum [0059](Example 5) Powder coating of the pin mill grinding thing of succinic acid was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of the joint liquid-1 prepared in Example 1 to crystalline cellulose (grain) (cell FIACP305: Asahi Chemical Industry). Powder coating of the milk sugar was carried out by CF GURANYU letter in a similar manner as a septum after desiccation.

[0060] Powder coating of the powder which mixed cimetidine and milk sugar by 1:1 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-1 prepared in Example 1 was coated with the fluid bed (STREA-1: Powrex) after desiccation.

[0061]- Formula core cell FIACP305 Ten 1st layer of part succinic acid 20 Part joint liquid-1 Seven 2nd layer of part milk sugar 60 Part joint liquid 25 3rd layer of part cimetidine 20 Part milk sugar 20 Part joint liquid-1 16 Part coat coating fluid-1 52 Part mean particle diameter 1000 - 1680 mum [0062]

(Comparative example 5) The pharmaceutical preparation shown in the following prepared by the same technique as Example 5 was obtained except using milk sugar instead of succinic acid.

[0063]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 5) of part

Milk sugar 80 Part joint liquid-1 32 The 2nd layer (the 3rd layer in Example 5) of part

Cimetidine 20 Part milk sugar 20 Part joint liquid-1 16 Part coat coating fluid-1 52 Part mean particle diameter 1000 - 1680 mum [0064](Comparative example 6) The septum of the pharmaceutical preparation equivalent to Example 1 was lost, and the pharmaceutical preparation shown in the following which added milk sugar of the part to the drug layer was obtained.

[0065]- Formula core cell FIACP305 Ten 1st layer of part tartaric acid 20 Part joint liquid-1 7.2 copies

of 2nd layer (the 3rd layer in Example 1)

TRM-115 40 Part milk sugar 100 Part joint liquid-1 86.4-copy coat coating fluid-1 50 Part mean particle diameter 1000 - 1680 μm [0066](Comparative example 7) The septum of the pharmaceutical preparation equivalent to Example 3 was lost, and the pharmaceutical preparation shown in the following which added milk sugar of the part to the drug layer was obtained.

[0067]- Formula core Nonpareil 103 30 1st layer of part tartaric acid 60 Part joint liquid-1 21 The 2nd layer (the 3rd layer in Example 3) of part

Quinine Ten Part milk sugar 200 Part joint liquid-1 90 Part coat coating fluid-1 270 Part mean particle diameter 1000 - 1680 μm [0068](Comparative example 8) The septum of the pharmaceutical preparation equivalent to Example 4 was lost, and the pharmaceutical preparation shown in the following which added milk sugar of the part to the drug layer was obtained.

[0069]- Formula core cell FIACP305 Ten 1st layer of part citrate 40 Part joint liquid-1 14 The 2nd layer (the 3rd layer in Example 4) of part

Noscapine Five Part milk sugar 65 Part joint liquid-1 33.9-copy coat coating fluid-1 28 Part mean particle diameter 1000 - 1680 μm [0070](Comparative example 9) The septum of the pharmaceutical preparation equivalent to Example 5 was lost, and the pharmaceutical preparation shown in the following which added milk sugar of the part to the drug layer was obtained.

[0071]- Formula core cell FIACP305 Ten 1st layer of part succinic acid 20 Part joint liquid-1 Seven The 2nd layer (the 3rd layer in Example 5) of part

Cimetidine 20 Part milk sugar 80 Part joint liquid-1 41 Part coat coating fluid-1 52 Part mean particle diameter 1000 - 1680 μm [0072](Example 1 of an examination) According to the elution test (the 2nd method) given in the 12th amendment Pharmacopoeia of Japan, the elution rate after specified time elapse was measured under the following test condition, respectively per each pharmaceutical preparation of Examples 1-5 and the comparative examples 1-5 which carried out the elution test above-mentioned preparation.

[0073]The elution test concerned examines elution of the drug from pharmaceutical preparation, and performed the 1st liquid supposing gastric juice, and the 2nd liquid supposing intestinal juice as test liquid.

[0074]- test condition test liquid: -- 900 ml of 2nd liquid (pH 6.8) number-of-rotations [of 900 ml of the 1st liquid (pH 1.2)]: -- 50 rpm [0075]a measuring condition -- Example 1, Example 2, the comparative example 1, and the comparative example 2 -- as for UV300nm, Example 3, and the comparative example 3, UV235nm, Example 4, and the comparative example 4 measured UV240nm, Example 5, and the comparative example 5 in UV230nm at the time of UV250nm and the 2nd liquid use at the time of the 1st liquid use.

[0076]Example 1 and the comparative example 1 -- as for drawing 2, Example 3, and the comparative example 3, in drawing 1, Example 2, and the comparative example 2, drawing 3, Example 4, and the comparative example 4 show drawing 5 the result, as for drawing 4, Example 5, and the comparative example 5.

[0077]By drawing 1 - 5, the example was not looked at by the 1st liquid and the 2nd liquid, and the difference was not looked at by elution nature as the result showed, but although the 1st liquid showed the same elution nature as an example according to the comparative example, the difference was clearly seen to elution nature with the 2nd liquid. That is, after both pharmaceutical preparation moves to intestines although a constant rate of drugs are emitted while being in the stomach, in the pharmaceutical preparation of a comparative example, it can expect that a drug is hardly emitted but bioavailability falls.

[0078](Example 2 of an examination) After making three oral absorption examination male beagles (weight of 10-12 kg) abstain from food one whole day and night and carrying out a food intake, the pharmaceutical preparation of Example 1 was prescribed for the patient so that the dose of a drug (TRM-115) might become in kg and 3.2mg / l, and the plasma concentration of the drug was measured temporally. The drug holidays for two weeks were set and it examined similarly using the comparative example 1. A result is shown in Table 1 (Cmax shows maximum blood concentration among front, and

AUC shows a blood-drug-concentration area under the curve).

[0079]

[Table 1]

表1 薬物の血漿中濃度の経時的変化

	Cmax	AUC
実施例1	0.252 µg/ml	1.366 µg·h/ml
比較例1	0.157 µg/ml	0.625 µg·h/ml

[0080]In the comparative example 1 in which organic acid is not prescribed, Cmax and AUC were cut lower than Example 1 in which organic acid is prescribed so that clearly from Table 1.

[0081](Example 3 of an examination) The aluminum package of the granulation of Example 1 and the comparative example 6 was carried out, and it saved at 40 **, and sampled temporally, and a fixed quantity and color difference were measured. color difference [as opposed to / measurement of color difference takes granulation in a granular material cell (CR-A50: Minolta Camera), and / an initial using a color difference meter (CR-200: Minolta Camera)] (deltaE) -- a table -- the bottom. A result is shown in Table 2. A fixed quantity was performed by HPLC and expressed the time of a start as 100%.

[0082]

[Table 2]

表2 40℃3カ月保存時の安定性-1

	定量値	色差 (ΔE)
実施例1	100.0%	1.42
実施例3	100.1%	1.62
実施例4	100.0%	1.11
実施例5	99.8%	1.57
比較例6	97.5%	10.52
比較例7	91.8%	18.22
比較例8	95.8%	16.23
比較例9	93.8%	10.56

[0083]most examples which have a septum between a drug and organic acid so that clearly from Table 2 -- although coloring was not seen, it was remarkably colored by the comparative example without a septum.

[0084]

[Effect of the Invention]By this invention, the drug and organic acid in which elution nature falls in a neutral region can be comred, and the medicinal preparation covered with the coat which consists of a high molecular compound of insoluble in water nature further can be provided. Furthermore, a granulation is carried out by this invention so that the drug and organic acid in which elution nature falls in said neutral region may not contact mutually by a septum, and the medicinal preparation covered with the coat which consists of a high molecular compound of insoluble in water nature can be provided.

[0085]The medicinal preparation of this invention can be concerned with pH and share stress in an alimentary canal in the drug with which water solubility falls in a neutral region, and an absorptivity falls at the time of internal use for this reason, can emit a fixed drug [be / nothing], and has the stability which was moreover excellent in the pharmaceutical preparation itself.

[0086]Therefore, the medicinal preparation of this invention can be used effective in the medicinal

preparation which uses as the main ingredients basic drugs, such as a thiourea derivative, noscapine, quinine, cimetidine, etc. which have the antibacterial action and antiulcer action to various drugs, especially HEKORIBAKUTA pylori.

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TECHNICAL FIELD

[Industrial Application]This invention relates to the medicinal preparation which can control discharge of a drug in order to acquire the continuous effect of a drug. It is concerned with pH and share stress in an alimentary canal, discharge of a fixed drug [be / nothing] can do the drug with which water solubility falls in a neutral region, and an absorptivity falls in detail at the time of internal use for this reason, and it is related with the medicinal preparation which was excellent in improvement in the stability for aiming at effective use of a drug, and a discharge rate further.

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EFFECT OF THE INVENTION

[Effect of the Invention]By this invention, the drug and organic acid in which elution nature falls in a neutral region can be corned, and the medicinal preparation covered with the coat which consists of a high molecular compound of insoluble in water nature further can be provided. Furthermore, a granulation is carried out by this invention so that the drug and organic acid in which elution nature falls in said neutral region may not contact mutually by a septum, and the medicinal preparation covered with the coat which consists of a high molecular compound of insoluble in water nature can be provided.

[0085]The medicinal preparation of this invention can be concerned with pH and share stress in an alimentary canal in the drug with which water solubility falls in a neutral region, and an absorptivity falls at the time of internal use for this reason, can emit a fixed drug [be / nothing], and has the stability which was moreover excellent in the pharmaceutical preparation itself.

[0086]Therefore, the medicinal preparation of this invention can be used effective in the medicinal preparation which uses as the main ingredients basic drugs, such as a thiourea derivative, noscapine, quinine, cimetidine, etc. which have the antibacterial action and antiulcer action to various drugs, especially HEKORIBAKUTA pylori.

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TECHNICAL PROBLEM

[Description of the Prior Art]When it is the drug that water solubility falls in a neutral region, as a method of securing the solubility, the technique in which a solid solution is made to form is known. There is an example which blends a drug into a high molecular compound and is used as the sustained release drug as an amorphous state as a means to gradual-release-ize a drug using this method. However, it was difficult for the solid dispersing element for the solubility of the high molecular compound which constitutes it to rule over, or for the solubility by the side of acidity to be too high under the influence of gastric acid, or to secure stability.

[0003]As a method of gradual-release-izing, the salts which have a drug and a buffer action in the coat of insoluble in water nature polymers are blended, The method of using and gradual-release-izing that the solubility of a drug falls according to the increase in an organic acid content is known by blending organic acid with diclofenac sodium as the discharging control pharmaceutical preparation which is not influenced by pH by making pH in a coat regularity, and same art. however, such art -- any -- although - it is the method of reducing solubility to a constant level, and is the method of raising the solubility of the drug that solubility falls in a neutral region, and the gradual-release-ized pharmaceutical preparation is not known.

[0004]Therefore, the purpose of this invention is to provide the medicinal preparation which can guarantee the bioavailability which was excellent in stability, could avoid refractory-ization in the neutral region of the drugs by which solubility falls in a neutral region, raised the absorptivity within an alimentary canal, and was excellent.

[Translation done.]

with a basic drug which reacts to organic acid and is disassembled by one side, a septum contributes to reservation of stability in a state of preservation.

[0017]By what a relation of a coat which consists of organic acid, a drug, and a high molecular compound considers as structure which serves as a coat which consists of an organic acid-drug-high molecular compound toward the outside from the central part in medicinal preparation of this invention. Dissolved organic acid can dissolve a drug efficiently, a coat which consists of high molecular compounds can be made to pass and emit, and utility of organic acid is lost. Organic acid which a part dissolved as it is a reverse structure will not pass along a drug layer, but will be emitted, and does not contribute to the dissolution of a drug.

[0018]In medicinal preparation of this invention, although it is also possible to make this organic acid into an acid salt, since a lot of salts are needed as compared with organic acid, it becomes large-sized manufacturing medicine, in order to acquire sufficient solubility of a drug, and administration becomes difficult, usefulness of organic acid is more expensive.

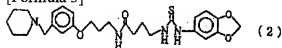
[0019]By making it structure mentioned above, a drug unstable to organic acid can also carry out [****]-izing of the medicinal preparation of this invention so that a drug may moreover be used effectively easily.

[0020]It is not a thing limited in any way as a drug mainly used for medicinal preparation of this invention, and a drug with which water solubility falls in a neutral region is mentioned. Basic drugs still more specifically expressed with a general formula (1), such as a thiourea derivative, noscapine, quinine, and cimetidine, are mentioned.

[0021]A thiourea derivative used by this invention mentioned above is crystalline powder which has an antibacterial action and an antiulcer action to HEKORIBAKUTA pylori, and, generally is poorly soluble in a neutral region. TRM-115 expressed with the following general formula (2) as a classic example of this thiourea derivative, for example is mentioned.

[0022]

[Formula 3]



[0023]As organic acid used for this invention, if nonpoisonous to a living body, it will be good, for example, succinic acid, tartaric acid, citrate, malic acid, etc. will be raised. The loadings of organic acid should have only the quantity in which a drug is dissolved in a polymers coat, and, generally 50 or more weight sections of organic acid should just be in a drug to 100 weight sections.

[0024]As a high molecular compound of insoluble in water nature used as a coat used for this invention, an ethyl acrylate methacrylate [methyl] copolymer emulsion (marketing name: --OIDORAGITTON30D.) Rehm Pharma, ethyl cellulose, polyvinyl acetate, polyvinyl chloride, Although an aminoalkylmetaacrylatecopolymer etc. are dissolved with a high pH solution (pH 6.5 or more), insoluble hydroxypropylmethylcellulose acetate succinate, methacrylic acid, a methyl acrylate copolymer, etc. are raised to water.

[0025]Within the limits of a limit defined by person skilled in the art, quantity (only coat) of a high molecular compound of insoluble in water nature can be fluctuated. Specifically, it is 1 to 30 % of the weight more preferably one to 50% of the weight to a granulation thing.

[0026]In medicinal preparation of this invention, although not limited at all as a microscopic septum between a drug and organic acid, powder coating, coating of a membrane formation nature substance, etc. are mentioned, for example.

[0027]As an ingredient which can be used for powder coating, what is necessary is just an excipient generally used for drugs, and milk sugar, starch, white soft sugar, grape sugar, mannitol, xylitol, sorbitol, crystalline cellulose, talc, etc. are mentioned.

[0028]The membrane formation nature substance should just be avirulence for a living body, for example, hydroxypropylcellulose, hydroxypropylmethylcellulose, methyl cellulose, a polyvinyl

pyrrolidone, etc. are mentioned.

[0029]Otherwise in a coating agent as a septum mentioned above, acetylation monoglyceride, such as a plasticizer, Diethyl phthalate, a triacetin, triethyl citrate, acetyl triethyl citrate, tributyl citrate, propylene glycol, tributyrin, a polyethylene glycol, dibutyl sebacate, castor oil, etc. may be added. Talc, titanium oxide, etc. may be added as an antibonding agent.

[0030]Pharmaceutical preparation of immediate releasability [medicinal preparation / of this invention] (whether a soluble film is used for a coat of this medicinal preparation.) Gradual release speed is also controllable by mixing arbitrarily pharmaceutical preparation which covers a gradual release coat thinly or does not cover a coat (as a capsule etc. which filled a granule and this granule in a capsule) to such an extent that a releasing speed is not influenced.

[0031]Medicinal preparation of this invention is mainly used as an orally administered drug.

[0032]When considering it as pharmaceutical preparation generally used widely, such as a capsule for taking orally to Homo sapiens, and granulation, as a concrete dosage form of medicinal preparation of this invention, it is considered as spherical particles 500-2000 micrometers in diameter, and a method of filling up one capsule with hundreds of particles, and prescribing them for the patient, etc. are mentioned. It can be considered as a forcible administration agent for animals as a pill about 10 mm in diameter, or can use as drugs for fish as a sphere 10 cm in diameter.

[0033]A process of medicinal preparation of this invention is not limited in any way, and all of a mixing method of a drug, a formation method of a septum, a coating method of a coat, etc. can be performed in accordance with a publicly known conventional method.

[0034]Powder coating of an organic acid layer, a barrier layer, and the drug layer is carried out in layers, carrying out the spray of the joint liquid to a spherical nuclear material as a concrete example, and a method of finally coating a polymers coat of insoluble in water nature is mentioned.

[Translation done.]

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EXAMPLE

[Example]Hereafter, an example is shown and this invention is explained still in detail.

[0036](Example 1) Hydroxypropylcellulose was melted in dehydrated ethanol and 5% (w/w) of joint liquid-1 was obtained. Powder coating of the pin mill grinding thing of tartaric acid was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of joint liquid-1 to crystalline cellulose (grain) (cell FIACP305: Asahi Chemical Industry).

[0037]Powder coating of the milk sugar was carried out after desiccation, using CF GURANYU letter similarly as a septum. Powder coating of the powder which mixed TRM-115 and milk sugar by 1:1 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-1 containing OIDORAGITTO NE30D was coated with the fluid bed (STREA-1: Powrex) after desiccation, and the pharmaceutical preparation shown below was obtained.

[0038]- Joint liquid-1 hydroxypropylcellulose Five Part dehydrated ethanol 95 Part [0039]- Coating fluid-1 OIDORAGITTO NE30D 100 Part talc 30 Part purified water 170 Part [0040]- Formula core cell FIACP305 Ten 1st layer of part tartaric acid 20 Part joint liquid-1 7.2 copies of 2nd layer (septum) Milk sugar 60 Part joint liquid-1 26.4-copy TRM[3rd layer]-115 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-1 50 Part mean particle diameter 1000 - 1680 mum [0041](Comparative example 1) The pharmaceutical preparation shown in the following prepared by the same technique as Example 1 was obtained except using milk sugar instead of tartaric acid.

[0042]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 1) of part

Milk sugar 30 Part joint liquid-1 33.6 copies of 2nd layer (the 3rd layer in Example 1)

TRM-115 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-1 50 Part mean particle diameter 1000 - 1680 mum [0043](Example 2) Powder coating of the pin mill grinding thing of tartaric acid was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of the joint liquid-1 prepared in Example 1 to crystalline cellulose (grain) (cell FIACP305: Asahi Chemical Industry). Powder coating of the milk sugar was carried out after desiccation, using CF GURANYU letter similarly as a septum.

[0044]Powder coating of the powder which mixed TRM-115 and milk sugar by 1:1 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-2 containing ethyl cellulose 10NF was coated with the fluid bed (STREA-1: Powrex) after desiccation, and the pharmaceutical preparation shown below was obtained.

[0045]- Coating fluid-2 ethyl-cellulose 10NF 5 Part talc Four Part triethyl citrate Three Part ethanol 88 Part [0046]- Formula core cell FIACP305 Ten 1st layer of part tartaric acid 20 Part joint liquid-1 7.2 copies of 2nd layer (septum)

Milk sugar 60 Part joint liquid-1 26.4-copy TRM[3rd layer]-115 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-2 100 Part mean particle diameter 1000 - 1680 mum [0047](Comparative example 2) The pharmaceutical preparation shown in the following prepared by the same technique as Example 2 was obtained except using milk sugar instead of tartaric acid.

[0048]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 2) of

part

Milk sugar 30 Part joint liquid-1 33.6 copies of 2nd layer (the 3rd layer in Example 2)

TRM-115 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-2 100-copy mean particle diameter 1000 - 1680 μm [0049](Example 3) Powder coating of the pin mill grinding thing of tartaric acid was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of the joint liquid-1 prepared in Example 1 to Nonpareil 103 (Freund Industrial). Powder coating of the milk sugar was carried out after desiccation, using CF GURANYU letter similarly as a septum.

[0050] Powder coating of the powder which mixed milk sugar with quinine by 1:2 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-1 prepared in Example 1 was coated with the fluid bed (STREA-1: Powrex) after desiccation, and the pharmaceutical preparation shown below was obtained.

[0051]- Formula core Nonpareil 103 30 1st layer of part tartaric acid 60 Part joint liquid-1 21 The 2nd layer (septum) of part

Milk sugar 180 Part joint liquid-1 75 3rd layer of part quinine Ten Part milk sugar 20 Part joint liquid-1 15 Part coat coating fluid-1 270 Part mean particle diameter 1000 - 1680 μm [0052](Comparative example 3) The pharmaceutical preparation shown in the following prepared by the same technique as Example 3 was obtained except using milk sugar instead of tartaric acid.

[0053]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 3) of part

Milk sugar 30 Part joint liquid-1 33.6 copies of 2nd layer (the 3rd layer in Example 3)

Quinine 40 Part milk sugar 40 Part joint liquid-1 60 Part coat coating fluid-1 100 Part mean particle diameter 1000 - 1680 μm [0054](Example 4) Powder coating of the pin mill grinding thing of citrate was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of the joint liquid-1 prepared in Example 1 to crystalline cellulose (grain) (cell FIACP305: Asahi Chemical Industry). Powder coating of the milk sugar was carried out after desiccation, using CF GURANYU letter similarly as a septum.

[0055] Powder coating of the powder which mixed nospapine and milk sugar by 1:1 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-1 prepared in Example 1 was coated with the fluid bed (STREA-1: Powrex) after desiccation, and the pharmaceutical preparation shown below was obtained.

[0056]- Formula core cell FIACP305 Ten 1st layer of part citrate 40 Part joint liquid-1 14 The 2nd layer (septum) of part

Milk sugar 60 Part joint liquid-1 The 26.4-copy 3rd layer nospapine Five Part milk sugar Five Part joint liquid-1 7.5-copy coat coating fluid-1 28 Part mean particle diameter 1000 - 1680 μm [0057]

(Comparative example 4) The pharmaceutical preparation shown in the following prepared by the same technique as Example 4 was obtained except using milk sugar instead of citrate.

[0058]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 4) of part

Milk sugar 100 Part joint liquid-1 40.4 copies of 2nd layer (the 3rd layer in Example 4)

Nospapine Five Part milk sugar Five Part joint liquid-1 7.5-copy coat coating fluid-1 28 Part mean particle diameter 1000 - 1680 μm [0059](Example 5) Powder coating of the pin mill grinding thing of succinic acid was carried out using CF granulator (CF360: Freund Industrial), carrying out the spray of the joint liquid-1 prepared in Example 1 to crystalline cellulose (grain) (cell FIACP305: Asahi Chemical Industry). Powder coating of the milk sugar was carried out by CF GURANYU letter in a similar manner as a septum after desiccation.

[0060] Powder coating of the powder which mixed cimetidine and milk sugar by 1:1 further was carried out by CF GURANYU letter in a similar manner after desiccation. Coating fluid-1 prepared in Example 1 was coated with the fluid bed (STREA-1: Powrex) after desiccation.

[0061]- Formula core cell FIACP305 Ten 1st layer of part succinic acid 20 part joint liquid-1 7 2nd layer of part milk sugar 60 Part joint liquid 25 3rd layer of part cimetidine 20 Part milk sugar 20 Part joint liquid-1 16 Part coat coating fluid-1 52 Part mean particle diameter 1000 - 1680 μm [0062]

(Comparative example 5) The pharmaceutical preparation shown in the following prepared by the same technique as Example 5 was obtained except using milk sugar instead of succinic acid.

[0063]- Formula core cell FIACP305 Ten The 1st layer (the 1st layer and the 2nd layer in Example 5) of part

Milk sugar 80 Part joint liquid-1 32 The 2nd layer (the 3rd layer in Example 5) of part
Cimetidine 20 Part milk sugar 20 Part joint liquid-1 16 Part coat coating fluid-1 52 Part mean particle diameter 1000 - 1680 μm [0064](Comparative example 6) The septum of the pharmaceutical preparation equivalent to Example 1 was lost, and the pharmaceutical preparation shown in the following which added milk sugar of the part to the drug layer was obtained.

[0065]- Formula core cell FIACP305 Ten 1st layer of part tartaric acid 20 Part joint liquid-1 7.2 copies of 2nd layer (the 3rd layer in Example 1)

TRM-115 40 Part milk sugar 100 Part joint liquid-1 86.4-copy coat coating fluid-1 50 Part mean particle diameter 1000 - 1680 μm [0066](Comparative example 7) The septum of the pharmaceutical preparation equivalent to Example 3 was lost, and the pharmaceutical preparation shown in the following which added milk sugar of the part to the drug layer was obtained.

[0067]- Formula core Nonpareil 103 30 1st layer of part tartaric acid 60 Part joint liquid-1 21 The 2nd layer (the 3rd layer in Example 3) of part

Quinine Ten Part milk sugar 200 Part joint liquid-1 90 Part coat coating fluid-1 270 Part mean particle diameter 1000 - 1680 μm [0068](Comparative example 8) The septum of the pharmaceutical preparation equivalent to Example 4 was lost, and the pharmaceutical preparation shown in the following which added milk sugar of the part to the drug layer was obtained.

[0069]- Formula core cell FIACP305 Ten 1st layer of part citrate 40 Part joint liquid-1 14 The 2nd layer (the 3rd layer in Example 4) of part

Noscapine Five Part milk sugar 65 Part joint liquid-1 33.9-copy coat coating fluid-1 28 Part mean particle diameter 1000 - 1680 μm [0070](Comparative example 9) The septum of the pharmaceutical preparation equivalent to Example 5 was lost, and the pharmaceutical preparation shown in the following which added milk sugar of the part to the drug layer was obtained.

[0071]- Formula core cell FIACP305 Ten 1st layer of part succinic acid 20 Part joint liquid-1 Seven The 2nd layer (the 3rd layer in Example 5) of part

Cimetidine 20 Part milk sugar 80 Part joint liquid-1 41 Part coat coating fluid-1 52 Part mean particle diameter 1000 - 1680 μm [0072](Example 1 of an examination) According to the elution test (the 2nd method) given in the 12th amendment Pharmacopoeia of Japan, the elution rate after specified time elapse was measured under the following test condition, respectively per each pharmaceutical preparation of Examples 1-5 and the comparative examples 1-5 which carried out the elution test above-mentioned preparation.

[0073]The elution test concerned examines elution of the drug from pharmaceutical preparation, and performed the 1st liquid supposing gastric juice, and the 2nd liquid supposing intestinal juice as test liquid.

[0074]- test condition test liquid: -- 900 ml of 2nd liquid (pH 6.8) number-of-rotations [of 900 ml of the 1st liquid (pH 1.2)]: -- 50 rpm [0075]a measuring condition -- Example 1, Example 2, the comparative example 1, and the comparative example 2 -- as for UV300nm, Example 3, and the comparative example 3, UV235nm, Example 4, and the comparative example 4 measured UV240nm, Example 5, and the comparative example 5 in UV230nm at the time of UV250nm and the 2nd liquid use at the time of the 1st liquid use.

[0076]Example 1 and the comparative example 1 -- as for drawing 2, Example 3, and the comparative example 3, in drawing 1, Example 2, and the comparative example 2, drawing 3, Example 4, and the comparative example 4 show drawing 5 the result, as for drawing 4, Example 5, and the comparative example 5.

[0077]By drawing 1 - 5, the example was not looked at by the 1st liquid and the 2nd liquid, and the difference was not looked at by elution nature as the result showed, but although the 1st liquid showed the same elution nature as an example according to the comparative example, the difference was clearly

seen to elution nature with the 2nd liquid. That is, after both pharmaceutical preparation moves to intestines although a constant rate of drugs are emitted while being in the stomach, in the pharmaceutical preparation of a comparative example, it can expect that a drug is hardly emitted but bioavailability falls.

[0078](Example 2 of an examination) After making three oral absorption examination male beagles (weight of 10-12 kg) abstain from food one whole day and night and carrying out a food intake, the pharmaceutical preparation of Example 1 was prescribed for the patient so that the dose of a drug (TRM-115) might become in kg and 3.2mg /, and the plasma concentration of the drug was measured temporally. The drug holidays for two weeks were set and it examined similarly using the comparative example 1. A result is shown in Table 1 (Cmax shows maximum blood concentration among front, and AUC shows a blood-drug-concentration area under the curve).

[0079]

[Table 1]

表1 薬物の血漿中濃度の経時的変化

	Cmax	AUC
実施例1	0.252 µg/ml	1.366 µg·h/ml
比較例1	0.157 µg/ml	0.625 µg·h/ml

[0080]In the comparative example 1 in which organic acid is not prescribed, Cmax and AUC were cut lower than Example 1 in which organic acid is prescribed so that clearly from Table 1.

[0081](Example 3 of an examination) The aluminum package of the granulation of Example 1 and the comparative example 6 was carried out, and it saved at 40 **, and sampled temporally, and a fixed quantity and color difference were measured. color difference [as opposed to / measurement of color difference takes granulation in a granular material cell (CR-A50: Minolta Camera), and / an initial using a color difference meter (CR-200: Minolta Camera)] (deltaE) -- a table -- the bottom. A result is shown in Table 2. A fixed quantity was performed by HPLC and expressed the time of a start as 100%.

[0082]

[Table 2]

表2 40℃3ヵ月保存時の安定性-1

	定量値	色差 (ΔE)
実施例1	100.0%	1.42
実施例3	100.1%	1.62
実施例4	100.0%	1.11
実施例5	99.8%	1.57
比較例6	97.5%	10.52
比較例7	91.8%	18.22
比較例8	95.8%	16.23
比較例9	93.8%	10.56

[0083]most examples which have a septum between a drug and organic acid so that clearly from Table 2 -- although coloring was not seen, it was remarkably colored by the comparative example without a septum.

[0084]

[Translation done.]

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1]The result of the elution test of the drug (TRM-115) of the pharmaceutical preparation of Example 1 and the comparative example 1 is shown.

[Drawing 2]The result of the elution test of the drug (TRM-115) of the pharmaceutical preparation of Example 2 and the comparative example 2 is shown.

[Drawing 3]The result of the elution test of the drug (quinine) of the pharmaceutical preparation of Example 3 and the comparative example 3 is shown.

[Drawing 4]The result of the elution test of the drug (noscapine) of the pharmaceutical preparation of Example 4 and the comparative example 4 is shown.

[Drawing 5]The result of the elution test of the drug (cimetidine) of the pharmaceutical preparation of Example 5 and the comparative example 5 is shown.

[Translation done.]

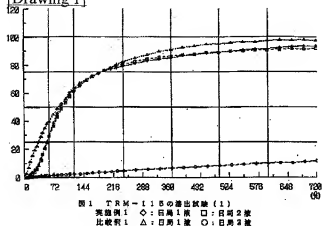
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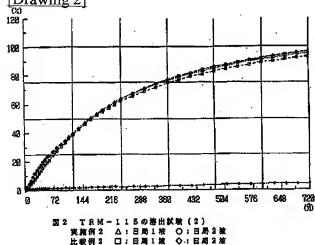
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DRAWINGS

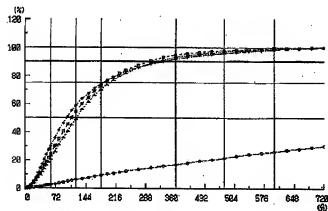
[Drawing 1]



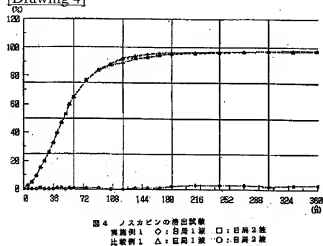
[Drawing 2]



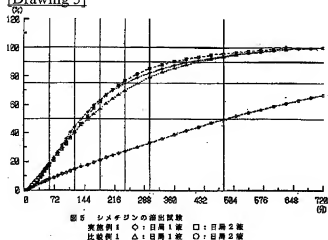
[Drawing 3]



[Drawing 4]



[Drawing 5]



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WRITTEN AMENDMENT

----- [A written amendment]

[Filing date]December 12, Heisei 6

[The amendment 1]

[Document to be Amended]Specification

[Item(s) to be Amended]0042

[Method of Amendment]Change

[Proposed Amendment]

[0042]- Formula

Core

Cell FIACP305 Ten Part

The 1st layer (the 1st layer and the 2nd layer in Example 1)

Milk sugar 80 Part

Joint liquid-1 33.6 copies

The 2nd layer (the 3rd layer in Example 1)

TRM-115 40 Part

Milk sugar 40 Part

Joint liquid-1 60 Part

Coat

Coating fluid-1 50 Part

Mean particle diameter 1000 - 1680 μm

[Amendment 2]

[Document to be Amended]Specification

[Item(s) to be Amended]0048

[Method of Amendment]Change

[Proposed Amendment]

[0048]- Formula

Core

Cell FIACP305 Ten Part

The 1st layer (the 1st layer and the 2nd layer in Example 2)

Milk sugar 80 Part

Joint liquid-1 33.6 copies

The 2nd layer (the 3rd layer in Example 2)

TRM-115 40 Part

Milk sugar 40 Part

Joint liquid-1 60 Part

Coat

Coating fluid-2 100 Part

Mean particle diameter 1000 - 1680 mum
[Amendment 3]
[Document to be Amended]Specification
[Item(s) to be Amended]0053
[Method of Amendment]Change
[Proposed Amendment]
[0053]- Formula
Core
Nonpareil 30 Part
The 1st layer (the 1st layer and the 2nd layer in Example 3)
Milk sugar 240 Part
Joint liquid-1 96 Part
The 2nd layer (the 3rd layer in Example 3)
Quinine Ten Part
Milk sugar 20 Part
Joint liquid-1 15 Part
Coat
Coating fluid-1 270 Part
Mean particle diameter 1000 - 1680 mum

[Translation done.]